activity as an association of engineers, that is, as a strictly or even quasi professional organization, but from its relations with the other sections, and that its own activities might well be somewhat curtailed if more intimate relations could be initiated and stimulated with those other sections; and that it should endeavor to present to its members not technical engineering subjects, but rather scientific subjects in branches seldom discussed in the technical engineering societies. Let us remember, then, that engineering is a profession, but that it is founded upon science; that the engineer should be at heart a true scientist, and thoroughly imbued with the scientific spirit. Further, that this association is not a professional society, but a scientific one, and that we come here rather as scientists than as engineers; that through our meetings and our contact with scientists in all branches, we may go forth to our daily practical and business work more thoroughly imbued than ever with a sense of the importance of our profession, and better able to apply economically the materials, forces and laws of nature in the service of man.

GEORGE F. SWAIN
HARVARD UNIVERSITY

THE CHEMICAL REGULATION OF THE PROCESSES OF THE BODY BY MEANS OF ACTIVATORS, KINASES AND HORMONES[1]

AT the time of Sir Charles Bell physiologists were beginning to realize the great importance of the nervous system as a mechanism for regulating and coordinating the varied activities of the body. To use his own expression, "The knowledge of what is termed the economy of an animal body is to be acquired only by an intimate acquaintance with the distribution and uses of the nerves." Since his time experimental investigations in physiology and clinical studies upon man have combined to accumulate a large fund of information in regard to the regulations and correlations effected through nervous reflexes. No one can doubt that very much remains to be accomplished along these same lines, but in recent years we have come to understand that the complex of activities in the animal body is united into a functional harmony, not only through a reflex control exerted by the nervous system, but also by means of a chemical regulation effected through the blood or other liquids of the organism. The first serious realization of the importance of this second method of regulation came with the development of our knowledge of the internal secretions during the last decade of the nineteenth century. The somewhat meager information possessed at that time in regard to these secretions developed in the fertile imagination of Brown-Séquard to a great generalization, according to which every tissue of the body in the course of its normal metabolism furnishes material to the blood that is of importance in regulating the activities of other tissues. This idea found a general support in the facts brought to light in relation to the physiological activities of the so-called ductless glands, and subsequently in the series of remarkable discoveries which we owe to the new science of immunology. In recent years it has been restated in attractive form by Schiefferdecker in his theory of the symbiotic relationship of the tissues of the body. According to this author we may conceive that among the tissues of a single organism the principle of a struggle for existence, which is so important as regards the relations of one organism to another, is re-

[1] Address of the vice-president and chairman of Section K—Physiology and Experimental Medicine. American Association for the Advancement of Science, Boston, December 28, 1909.

placed for the most part by a kind of symbiosis, such that the products of metabolism in one tissue serve as a stimulus to the activities of other tissues. If a muscle is stimulated to greater growth by an excess of functional activity the substances given off to the blood during its metabolism act favorably upon the growth of other muscles which are not directly concerned in the increased work, or upon the connective tissue surrounding and permeating the muscular mass; and conversely, the development of connective tissue from any cause aids directly by its secretions or excretions in the growth of the muscle. There is thus established a *circulus benignus* by means of which each tissue profits from the functional activity of its fellow tissues. From many sides and in many ways facts have been accumulating which tend to impress the general truth that the co-activity of the organs and tissues may be controlled through chemical changes in the liquid media of the body, as well as through nerve impulses, but in physiology at least we owe the definite formulation of this point of view to Bayliss and Starling. Through their investigations upon secretin they obtained an explicit example of how one organ controls the activity of another organ by means of a specific chemical substance given off to the blood. Other facts known in physiology in regard to the internal secretions were easily brought into line with this definite instance furnished by the secretin, and Starling's convenient term of "hormone," as a general designation for such substances, has served to give a wide currency to the conception. The word and the generalization implied by it have been adopted by investigators in many fields of biological research to explain phenomena of correlation which heretofore it has been impossible to bring under the general rubric of nervous reflexes; phenomena which in fact it has been difficult to express clearly in any precise way such as might serve to stimulate direct experimental investigation. An interesting example of this application of the term and the idea contained in it is found in the theory advanced by Cunningham to explain the development and inheritance of secondary sexual characteristics. This author constructs a system of hypothetical hormones which, if present, would account not only for the development of the secondary sexual characters, as the result of the action of specific hormones furnished by the reproductive cells, but would also make conceivable a method by which these secondary characters, like other somatogenic characters, might affect the germ cells in turn in such a definite way as to be transmitted to the following generations. It is not my purpose to criticize this or similar theories. They will doubtless serve a good purpose in stimulating and directing investigations. It does, however, seem probable that the term hormone, like some of the useful terminology of immunology, will be overworked, and that investigators may deceive themselves as well as others when they conclude that any given relationship is an example of hormone regulation. It has occurred to me that it may be useful in connection with this symposium upon the internal secretions to review very briefly the state of our knowledge in regard to the hormones, with the purpose of discussing somewhat the probable nature of their action and the extent of their distribution.

In treating this subject one must consider also the more or less nearly related instances of combined activity of a chemical sort which are expressed by such terms as chemical activators, kinases and co-ferments. These terms like that of hormone are relatively new, they have been brought

into existence by investigators to explain or to express special reactions connected with metabolism and particularly with the action of ferments. Their precise meaning must be determined by further knowledge of the facts they are intended to describe, but something may be gained by attempting to define them as they are used in physiology at present. The word activator has reference to the fact long known that the ferments, or some of them at least, are secreted in an inactive form, a proferment, which is activated or converted to an active form by a reaction with some definite substance produced elsewhere in the body. Pepsin, for example, is secreted as pepsinogen and is activated to pepsin by the hydrochloric acid formed by other gland cells. Calcium salts are necessary for the activation of the prothrombin, and enterokinase or calcium plays a similar rôle with reference to the trypsinogen. It is to be noted that reactions of this kind are not confined to the ferments. The typical hormone, secretin, exists in the form of an insoluble prosecretin which may be activated by acids, and, according to Delezenne, calcium takes an essential part in the activation of enterokinase, in somewhat the same way as occurs with thrombin. The nature of these activating reactions is not known. The view has been proposed that the inorganic constituents involved, the hydrochloric acid and the calcium for example, act as catalyzers which accelerate a reaction that would occur without their assistance. There is, however, no evidence to show that thrombin is formed in any amount in the absence of calcium salts, nor that pepsinogen yields pepsin without the presence of acids. As Bayliss has pointed out, these reactions belong to the irreversible group, and it is possible that the activator or one of its constituents is represented in the composition of the active substance that is formed. However that may be, it is to be noted that the process of activation is an instance of chemical coordination. The pepsin formed in one kind of gland cell is activated by the acid produced in a different variety of cell. The hydrochloric acid produced in the stomach is carried into the intestine with the flow of chyme and there activates the prosecretin of the intestinal epithelium either directly or indirectly. One tissue, in other words, through its products of metabolism aids another tissue in the performance of its functional duties.

The term kinase is used at present in animal physiology in connection with two reactions only. In both cases it refers to an activating process similar to those just considered, except that the activator is a colloidal substance of unknown composition. The pancreatic juice poured into the duodenum contains its proteolytic enzyme in the form of a trypsinogen which is activated immediately to trypsin by contact with the duodenal epithelium or with the secretion furnished by this epithelium. The activating substance is designated as enterokinase. It is present normally in the intestinal juice formed in this part of the alimentary canal, or it may be obtained in extracts of the mucous membrane of the duodenum or jejunum. According to Pawlow, however, the intestinal secretion obtained by direct mechanical stimulation of the epithelium is lacking in enterokinase. This latter substance is produced in fact only under the influence of some constituent of the pancreatic juice, possibly the trypsinogen itself. In other words it would seem that the enterokinase must itself be activated before it can fulfill its functions as an activator of the trypsinogen. The chain of inter-related processes occurring at this point in the act of digestion becomes somewhat intricate, as fol-

lows: Hydrochloric acid formed in the stomach and brought into the intestine with the chyme stimulates the epithelial cells of the intestine to form secretin and to pass it into the blood. The secretin conveyed by the blood to the pancreas stimulates this organ to secrete pancreatic juice. The pancreatic juice is carried to the duodenum and stimulates the epithelial cells to form enterokinase which then activates the trypsinogen to trypsin. Assuming that all of these steps are verified by future work, we have in this series of events an excellent example of chemical coordination, that is to say, of coordination effected by chemical stimuli conveyed from one organ to another through the liquids of the body. It may be noted in passing that the epithelial cells of the duodenum under the influence of acids or soaps form an internal secretion, the secretin, while under the influence of the pancreatic juice they produce an external secretion, the enterokinase. It is of course possible that these two different functions are subserved by separate cells, but so far as our evidence goes at present we must infer rather that one and the same epithelial cell gives either an internal or an external secretion according to the nature of the chemical stimulus acting upon it. While there can be no doubt at all of the existence of enterokinase and of its wonderful effect in activating almost instantaneously the trypsinogen of the pancreatic juice, much uncertainty prevails as to its nature and its mode of action. Pawlow thought that it belongs to the group of enzymes and this view has been supported in an almost convincing way by the experiments of Bayliss and Starling. In accordance with this view it is found that the substance exhibits a certain degree of thermolability, being destroyed at a temperature of 67 to 70° C., although in this respect it is less sensitive than most of the well-known enzymes. From this standpoint the action of the enterokinase upon the trypsinogen would come under the general head of catalytic reactions, but here again it is to be observed that its action differs from that of the other enzymes in the great rapidity with which it is completed, a rapidity quite comparable to that of ordinary chemical reactions. Other observers (Dastre and Stassano, Hamburger and Hekma, Cohnheim) have contended that the enterokinase unites permanently and quantitatively with the trypsinogen, after the manner of an amboceptor and complement, to form a new and active compound, the trypsin, and the whole reaction has been still further complicated by the discovery (Delezenne) that the trypsinogen may be activated by calcium salts without the presence of enterokinase. The action of the calcium requires some time for its development but when it occurs it takes place not gradually but abruptly, just as in the case of the activation produced by enterokinase. The further fact stated by Delezenne that the enterokinase itself needs the presence of calcium salts before it acquires the property of affecting trypsinogen suggests naturally the thought that the action of the enterokinase may be at bottom another case of calcium activation. Pozerski states that in the inactive pancreatic juice obtained by injections of secretin calcium is not present; whereas in the active juice following upon the use of pilocarpin, calcium is contained, and the digestive action of the juice runs parallel with the content in calcium. But whether the enterokinase acts as a ferment, or an amboceptor, or a calcium carrier it constitutes a special type of organic activator and this fact suggests the possibility that other processes in the body may be controlled by similar compounds.

At present only one other organic activator of this kind has been described, namely, the thrombokinase of blood coagulation. This hypothetical substance is given great importance in the theory of coagulation proposed by Morawitz. According to this theory the blood corpuscles under abnormal environment yield an unknown substance of colloidal nature which together with calcium is necessary for the complete activation of thrombin, and therefore for the clotting of blood. A similar kinase is furnished by the tissues in general, so that blood escaping from a vessel and coming in contact with the surrounding tissues obtains from them a kinase which accelerates the process of clotting. The evidence for the existence of this kinase is far less satisfactory than in the case of the enterokinase, indeed one may have serious doubts whether the facts at present warrant the assumption that a specific organic kinase must cooperate with the calcium in activating the thrombin, but if the idea is demonstrated to be correct it will furnish another very interesting example of the way in which chemical coordination may be employed in the body. In this case the blood may be supposed to stimulate the tissue cells to form a substance not directly of importance to their own activity, but which initiates the coagulation of the blood, stops the hemorrhage and thus saves the organism from destruction. The series of events is quite parallel to that described for the pancreatic juice and the enterokinase.

In addition to the activators of the inorganic and the colloidal type there is perhaps a third kind of activation exemplified in the substances known as coenzymes or coferments. This term may be used to define that kind of cooperative activity between an enzyme and some other non-colloidal substance which we see illustrated in the influence of the bile salts upon pancreatic lipase. The process differs from activation of a proferment to a ferment only in that the combination of the enzyme with its activator is dissociable instead of being permanent. By dialysis or otherwise the coenzyme can be separated from the enzyme and the action of the two may be tested separately or in combination. Perhaps this species of activation may be more common in the animal body then we have supposed. Bierry and Giaja have shown that the amylase of pancreatic juice loses its diastatic action entirely when dialyzed and this power or property is restored upon the addition of sodium chloride. It would seem from their experiments that the amylase is active only when combined with an acid ion, such as Cl or Br and the transition from one form to the other, from the active to the inactive or the reverse is easily accomplished. No one can doubt that all these forms of chemical activation are allied in a general way to the more interesting and obvious mode of chemical coordination illustrated by the hormones. Starling defines hormones as chemical messengers which formed in one organ travel in the blood stream to other organs of the body and effect correlation between the activities of the organ of origin and the organs on which they exert their specific effect. Such substances belong to the crystalloid rather than the colloid class, they therefore are thermostable and do not act as antigens when injected into the living animal. The general idea of this definition is clear and most suggestive, but in its details it is made especially to suit the case of secretin, and therefore may not fit so well for other substances of like physiological value. Conveyance through the blood stream, while certainly the most common occurrence for this class of bodies, ought not to constitute an essential part of their

definition. The secretin formed in the intestinal epithelial cell is conveyed to the pancreas in the blood and brings about a correlation between the activity of this gland and that of the duodenum, but on the other hand some substance contained in the pancreatic juice and conveyed to the duodenum in the stream of secretion excites the formation of the enterokinase, and thus correlates the activity of the duodenum with that of the pancreas. The two actions seem to be so similar, except for the means of transport, that one would naturally put them in the same class. By the same reasoning we might be justified in designating the hydrochloric acid of the gastric juice as a hormone in reference to its action in causing a formation of secretin in the epithelial cells of the duodenum. One can imagine that a similar transportation may occur in the secretions of the reproductive or respiratory passages, in the cerebro-spinal fluid, as seems to be the case for a time at least with the secretion of the pars intermedia of the pituitary gland, or even along the axial stream of a nerve fiber. If, as seems to me, the idea of correlation or coordination is the essential point rather than the assumption that the product must constitute an internal secretion, we might modify the definition so far as to designate as hormones those substances in solution which, conveyed from one organ to another through any of the liquid media of the body, effect a correlation between the activities of the organ of origin and the organ on which they exert their specific effect. As regards the nature of the action of the hormones on the organ affected we know too little to make any safe generalization. In the case of the secretin it seems most probable that the hormone arouses the pancreatic cells to an act of secretion and therefore it has in this instance the value of a chemical stimulus. But in other cases the effect of the hormone may be rather of the nature of an activation. This at least would seem to be true for the hormone, of unknown nature, given off by the pancreas and concerned in the glycolysis of sugar in the organism. The effect of the hormone adrenalin upon the musculature innervated by the sympathetic system may also be of the nature of an activation rather than of a chemical stimulation.

The substances of known composition which may be regarded as playing the rôle of hormones are few in number, three or four at most as follows: First, the carbon dioxide formed in the tissues, particularly in muscle during contraction. It seems agreed now that the carbon dioxide acts as the normal stimulus to the respiratory center. When produced in the working muscles in such quantities as to raise perceptibly the carbon dioxide tension in the alveoli of the lungs and the blood of the pulmonary veins, the respiratory center is excited to greater activity and the excess above the normal contents is thereby removed; second, the adrenalin of the adrenal glands which in some way, directly or indirectly, makes possible the full functional activity of the involuntary musculature of the body; third, the hydrochloric acid produced in the stomach which stimulates the formation of secretin in the duodenal epithelium; and fourth, possibly the iodothyrin of the thyroid gland with its dynamogenic effect upon the neuromuscular apparatus of the body. In addition there are a number of hormones of unknown composition which have been either proved or assumed to exist, and which are held responsible for certain well known correlations of function. The pancreatic secretin formed in the epithelium of the duodenum or jejunum which stimulates the flow of pancreatic secretion; the gastric

secretin formed in the plyoric mucous membrane which gives rise to the chemical secretion of gastric juice; a secretin formed in the duodenal epithelium which stimulates the formation of intestinal juice in the following segments of the intestine; unknown hormones of pancreatic origin which determine the absorption activity of the intestinal epithelium; vaso-dilator hormones formed in tissues in functional activity and which have a specific effect upon the vessels of the functioning organ; a vaso-constricting and a diuretic hormone formed in the posterior lobe of the pituitary body; a hormone controlling the growth of the bones and connective tissues produced in the anterior lobe of the pituitary body; a hormone controlling the oxidation of sugar in the body and produced in the cells of the islands of Langerhans in the pancreas; a hormone produced in the thymus which controls possibly in some way the development of the reproductive organs; a vaso-constricting hormone formed in the kidneys; a hormone in the salivary glands which controls the flow of water from the blood capillaries in the glands; a hormone produced in the fœtus in utero which stimulates the growth of the mammary glands; a hormone in the ovary which controls the growth of the uterus and the processes of menstruation; a hormone in the ovary which controls the implantation of the fertilized ovum and the growth of placental tissue; a hormone in the testis which initiates the development of the secondary sexual characteristics in the male; hormones of an indefinite number, produced in all the tissues and acting specifically upon the determinants in the gametes in such a way as to make possible the transmission of acquired characteristics. It is evident from this summary that there is a well developed tendency in physiology at the present day to utilize the conception of hormones to explain all relationships not otherwise intelligible. A few years ago the number of hypothetical enzymes in the body was likely to be increased whenever a new research in metabolism appeared, now the drift seems to be in the direction of manufacturing new hormones. This natural inclination to abuse a new and attractive idea will not of course prejudice us against the great importance of the suggestion which we owe to Bayliss and Starling. It is to be hoped only that no one will be tempted to give to these hypothetical hormones distinctive names, except in cases such as the secretin, adrenalin, etc., in which the substances have been isolated in some degree of purity. For once a specific name has become attached to an entirely unknown substance it acquires henceforth an easy currency in our literature, and soon many of us unconsciously assume that the thing so designated constitutes one of the verified facts of our science. By way of example one may cite the thrombokinase which has become such a familiar term in the literature of coagulation and which not infrequently is employed by writers as though its existence were a settled fact.

Among his other valuable suggestions regarding the characteristics of the hormones, Starling has called attention to the fact that some of them act by increasing the processes of disassimilation or catabolism, while others apparently stimulate the processes of assimilation or growth. In this latter group we may include the hormones of the anterior lobe of the pituitary body, according to the present conception of the functions of that gland, and all of the hormones of the reproductive cells. These latter have in general what has been designated as a dynamogenic action, they cause hypertrophies in various organs or tissues and invoke therefore processes of

synthesis rather than those of splitting and oxidation. Hypertrophy as an outcome of increased functional activity is a familiar phenomenon, but as Nussbaum remarks the hypertrophy induced by testicular or ovarian hormones resembles rather the effect of the growth energy exhibited by the developing embryo, in that it is dependent upon influences other than those arising from functional use. What these influences may be is at present a matter of pure speculation. In his recent most interesting contributions to our knowledge of growth Rubner has been led to assume that the property of growth in the young organism is connected with certain special chemical complexes in the protoplasmic material, complexes which have nothing directly to do with the simple maintenance of the nutrition of the cell and which after adult life is reached disappear for the most part from the general soma. In line with this hypothesis one might assume that the hormones given to the blood by the reproductive cells contain such complexes which when anchored in certain tissues lead to an accelerated growth. Perhaps the clearest and most interesting experiments made upon the reproductive hormones are those reported by Nussbaum. He chose for his experiments the males of *Rana fusca* whose reproductive organs go through a cyclical development each year. At the proper period the preparation for the mating season shows itself in the hypertrophy of the seminal vesicles, of the thumb pads and of certain muscles in the forearm. If the frog is castrated these hypertrophies do not occur, or if they have begun before the castration is performed retrogressive changes take place. On the other hand, the usual hypertrophy of the nuptial organs can be initiated in a castrated frog if pieces of the testis from another frog are introduced into the dorsal lymph sacs. The pieces thus introduced do not become grafted permanently but are gradually absorbed and the growth of the thumb pads and of the muscles in the forearms falls off after this absorption is completed. Nussbaum believes that the stimulating effect of the testicular hormones is not exerted directly upon the tissues which show the increased growth, but rather upon the portions of the central nervous system which innervate these tissues. This belief rests upon the experimental fact that if the peripheral nerves going to the glands and papillæ of the thumb pads are severed on one side the testicular hormone affects only the other intact side. This experiment and the conclusion drawn from it opens up the interesting question whether perhaps the reproductive hormones in general exert their effect through the central nervous system. This has not been the usual belief, and the experiments of Nussbaum are open to the obvious objection that the section of the peripheral nerves may have induced certain secondary changes in metabolism which indirectly antagonized the action of the testicular hormone. At present these experiments, so far as I know, have not been repeated with this objection in mind and it is somewhat gratuitous to criticize the author's conclusions until further work is reported.

William H. Howell
The Johns Hopkins University

SIR WILLIAM CROOKES[1]

The generation just passing away and that now enjoying the vigor of its beginning, are fortunate in this country, because they are recognizing the privileges and advantages of anniversary celebrations. The indulgence in

[1] Address of Professor Charles Baskerville before the Chemists' Club, Harvard Night, November 27, 1909, on which occasion Sir William Crookes was elected to honorary membership in the club.